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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/688,925	10/21/2003	Geertruida M. Veldman	08702.0020-00000	2555

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FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER
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EXAMINER

KEMMERER, ELIZABETH

ART UNIT	PAPER NUMBER
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1646

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/18/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No. 10/688,925	Applicant(s) VELDMAN ET AL.	
	Examiner Elizabeth C. Kemmerer, Ph.D.	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 September 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-11,30,33-35,37 and 41-51 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-11,30,33-35,37 and 41-51 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>3/24/04, 6/25/04, 6/15/05</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I in the reply filed on 29 September 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicant's election with traverse of the species of SEQ ID NO: 14 in the reply filed on 29 September 2006 is found to be persuasive. The species requirement is withdrawn to the extent that the following sequences will be examined: SEQ ID NOS: 14, 16, 18, 26, 28, and 30-36.

Status of Application, Amendments, And/Or Claims

The preliminary amendment of 29 September 2006 has been entered in full. Claims 1-11, 30, 33-35, 37, and 41-51 are under examination.

35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11 and 43-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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Claim 1 recites an isolated antibody or a fragment thereof comprising an amino acid sequence. It is not clear if the antibody or the fragment or both must comprising the recited sequence. Further, the end of claim 1 recites "capable of specifically binding GDF 8 or BMP 11." It is not clear if the phrase pertains to SEQ ID NO: 14, SEQ ID NO: 26, the fragments of SEQ ID NO: 14 or 26, or all of the above.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3 and 41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention appears to employ novel biological materials, specifically a deposited microorganism having ATCC Deposit Designation No. PTA 4741. Since the biological materials are essential to the claimed invention they must be obtainable by a repeatable method set forth in the specification or otherwise readily available to the public. If the biological materials are not so obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the biological materials. The specification does not disclose a repeatable process to obtain the biological materials

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and it is not apparent if the biological materials are readily available to the public. It is noted that Applicant has deposited the biological materials (p. 33 of the specification), but there is no indication in the specification as to public availability. If the deposit is made under the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific biological materials have been deposited under the Budapest Treaty and that the biological materials will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, and that the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer, would satisfy the deposit requirement made herein. If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. §§ 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;

(d) a test of the viability of the biological material at the time of deposit will be made (see 37 C.F.R. § 1.807); and

(e) the deposit will be replaced if it should ever become inviable.

Applicant's attention is directed to M.P.E.P. §2400 in general, and specifically to §2411.05, as well as to 37 C.F.R. § 1.809(d), wherein it is set forth that "the specification shall contain the accession number for the deposit, the date of the deposit, the name and address of the depository, and a description of the deposited material sufficient to specifically identify it and to permit examination."

Claims 1, 2, 4-11, 30, 33-35, 37, and 42-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a) an isolated antibody capable of specifically binding a vertebrate GDF-8 or a vertebrate BMP-11, said antibody comprising:

i) the amino acid sequence of SEQ ID NO: 14,

ii) the amino acid sequence of SEQ ID NO: 26,

iii) a fragment of SEQ ID NO: 14 that is capable of specifically binding a vertebrate GDF-8 or a vertebrate BMP-11, or

iv) a fragment of SEQ ID NO: 26 that is capable of specifically binding a vertebrate GDF-8 or a vertebrate BMP-11,

or

b) a fragment of a) that is capable of specifically binding a vertebrate GDF-8 or a vertebrate BMP-11, said fragment comprising:

- i) the amino acid sequence of SEQ ID NO: 14,
- ii) the amino acid sequence of SEQ ID NO: 26,
- iii) a fragment of SEQ ID NO: 14 that is capable of specifically binding a vertebrate GDF-8 or a vertebrate BMP-11, or
- iv) a fragment of SEQ ID NO: 26 that is capable of specifically binding a vertebrate GDF-8 or a vertebrate BMP-11,

does not reasonably provide enablement for other antibodies. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure enables one skilled in the art to make and use the claimed invention in its full scope without resorting to undue experimentation include: (1) the breadth of the claims; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature or complexity of the invention; (5) the state of the prior art; (6) the predictability or unpredictability of the art; (7) the relative skill of those in the art; and (8) the quantity of experimentation necessary. See *In re Wands*, 8 USPQ2d. 1400 (Fed. Cir. 1988).

In the instant case, the claims broadly encompass antibodies of any sequence that bind GDF-8 or BMP-11 from any organism. As discussed in the rejection under 35 U.S.C. § 112, second paragraph, above, claim 1 recites sequences and fragments thereof. It is not clear how long these fragments must be or whether or not they must retain activity. Therefore, the claims read on virtually any antibody of any sequence

(which would comprise a "fragment" of SEQ ID NO: 14 or 26 which is one amino acid in length) and any activity.

The specification provides ample guidance regarding antibodies of SEQ ID NO: 14 or 26. However, there is little guidance regarding antibodies of unrelated structure or function.

The working examples are limited to those pertaining to the antibodies of SEQ ID NO: 14 or 26.

The nature of the invention is very complex and unpredictable, involving antibodies and their interactions with their target antigens. The courts have long acknowledged that such inventions are complex and unpredictable. For example, as was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991).

The state of the art shows that vertebrate GDF-8 proteins are highly conserved and that antibodies can be made thereto, as acknowledged in the instant specification (e.g., pp. 1-2). However, the antibodies of SEQ ID NOS: 14 and 26 have been shown in this application to have special properties, such as inhibiting the binding of GDF-8 to ActRIIB. The prior art is silent with respect to other such antibodies. Furthermore, the

art acknowledges that minor changes in structure unpredictably affects function, including antibody specificity. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, *Biochemistry* 29:8509-8517; Ngo et al., 1994, *The Protein Folding Problem and Tertiary Structure Prediction*, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the

specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

While the level of skill in the art is admittedly high, the quantity of experimentation required to make and use the claimed invention in its full scope is quite large. Therefore, due to the large quantity of experimentation necessary, the lack of direction/guidance presented in the specification regarding antibodies other than those of SEQ ID NOS: 14 and 26, the absence of working examples directed to the same, the complex nature of the invention, the state of the prior art, the unpredictability of the interaction between any protein and any antibody, and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

No claims are allowed.

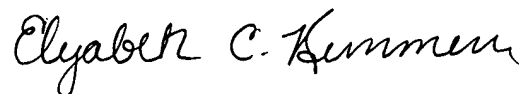
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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number is (571) 272-0874. The examiner can normally be reached on Monday through Thursday, 7:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D. can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ECK



ELIZABETH KEMMERER
PRIMARY EXAMINER